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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/722,049	11/25/2003	Michael Hennig	21491	3280

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EXAMINER	
NASHED, NASHAAT T	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 06/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/722,049	HENNIG ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *15-19* is/are withdrawn from consideration.

5)☒ Claim(s) *20* is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/27/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's election with traverse of Group I, claims 1-14 and 20, in the reply filed on May 25, 2006 is acknowledged. The traversal is on the ground(s) that searching the invention of Group I and II does not constitute a search burden on the examiner and that the restriction is contrary to public policy. This is not found persuasive. As indicated in the previous Office action, the invention of Group I and II are drawn to independent chemical entity having different structure and function, and as such require separate searches in the patent and non-patent literature. Invention II is classified in class 435, subclass 212 because of claims 18 and 19 directed to a method of making the polypeptide encoded by the nucleic acid of invention II using the nucleic acid. Thus, there is no burden of searching the nucleic acid and a method of its use, and therefore, the method is incorporated in invention II. Applicants are entitled for a method of making the polypeptide of SEQ ID NO: 2, if claim 20 is found allowable. See *in re* Ochiai and the paragraph bellow, which out line the requirement for rejoining claims of a method.

The requirement is still deemed proper and is therefore made FINAL.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Applicant petition under 37 CFR 1.84(a)(2) to request the acceptance of color drawing filed November 25, 2003 has been accepted.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s). Applicants' attention is directed to 37 CFR 1.821, which states:

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Thus, each time the specification refers to a specific protein, which its amino acid sequence disclosed in the sequence listing, the sequence identification number should accompany each recitation of the protein. See for example paragraph 65, line 1, paragraph 68, line 1, and paragraph 74, line 1. Applicants are responsible for identifying all instances where compliance is required and perfect their compliance with the sequence rules.

The disclosure is objected to because of the following informalities:

(a) The amendment filed June 1, 2004 contains undefined symbols such square, see for example, the amendment to paragraph 55 at page 3, line 2, 3 and 6; paragraph 89, and paragraph 98. It appears that all Greek letters in the original text are now squares; and

(b) The figure description for Figure 1 indicate that human DPP IV is that of SEQ ID NO: 3, but SEQ ID NO: 3 differs from that of Figure 1 by at least one amino acid residue. See the first few amino acids at the N-terminus of both sequences.

Appropriate correction is required.

New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application. Figure 1 is of poor quality after it was scanned and the examiner can't read part of the Figure such as the sequence within the black box and several segments of the sequence are completely or partially missing. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact

terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-8 are directed to all possible crystals of the extracellular domain of any mammalian DPP-IV and its complex with a ligand in the orthorhombic space group $P2_1 2_1 2_1$. Claims 9-14 are directed to a method of obtaining said crystal using PEG with an average molecular weight of 1000-20,000 at a concentration of 10% to 30% in the presence of 10%-20% glycerol at any pH and salt concentration.

The court of Appeals for the Federal Circuit has held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] name chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." UC California v. Eli Lilly (43 USPQ2d 1398). For claims drawn to genus, MPEP section 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Also, MPEP section 2163 states that a representative number of species mean that the species, which are adequately described, are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. At the time of invention, the full-length DPP-IV was well known in the art along with variants from other mammals as well as its biological role in regulating several biological processes. The instant application describes the crystallization of a modified fragment of human DPP-IV, presumably, consisting of the dipeptide glutamine-phenylalanine attached to the N-terminus of the amino acid sequence of SEQ ID NO: 2 (see paragraph 65) under the specific condition described in paragraph 74, bridging pages 23 and 24. In general, for a species of crystal to be adequately and structurally described, the following must be adequately described: (i) the exact chemical composition of the crystal, i.e., the structure feature of all molecules in the crystal including the amino acid sequence of any protein or nucleic acid, (ii) the space group of the crystal; and (iii) the unit cell dimension of the crystal. Neither the applicants nor the prior art has described a crystal or the crystallization of the extracellular domain of DPP-IV. Thus, the specification fails to describe additional representative species of these

crystals by any identifying structural characteristics or properties other than the space group in claim 1 and the broad range of cell dimension in claim 2 and 5. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to all-possible orthorhombic crystals in space group $P2_1\ 2_1\ 2_1$ comprising any extracellular domain from any mammalian DPP-IV having any amino acid sequence and containing any additional number of amino acid residues and method of its making. Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses all-possible orthorhombic crystals in space group $P2_1\ 2_1\ 2_1$ comprising any extracellular domain from any mammalian DPP-IV having any amino acid sequence and containing any additional number of amino acid residues and method of its making. The specification provides guidance and examples in the form of an assay to obtain a protein consisting, presumably, of the dipeptide glutamine-phenylalanine attached to the N-terminus of the amino acid sequence of SEQ ID NO: 2 under the specific condition in the paragraph bridging pages 23 and 24 (see examples 1 and 2). While molecular biological techniques and genetic manipulation to make any protein, a general crystallization methods for proteins, and synthetic method to make any compound that binds to DPP-IV are known in the prior art and the skill of the artisan are well developed, knowledge regarding crystallization of a particular protein and its complexes is lacking. It is well established in the art that obtaining a protein and its complexes in a crystal form is highly unpredictable without any clear expectation of success, and any change in a given crystallization condition including any minor alteration could alter the crystal form and its diffraction characteristics or even lack of crystal formation. It is now evident that protein crystallization is the major hurdle in protein structure determination. For this reason, protein crystallization has become a research subject in and of itself, and is not simply an extension of structure biologist or crystallographer's laboratory. There are many references that describe the difficulties associated with protein crystals. See for

example, Gilliland *et* al, (*Curr. Open in Struct. Biol.* 1996, 6, 595-603) in particular page 600, left column second paragraph; Ke *et al.* (Methods, 2004, 34, 408-414); and Wiencek, J. M. (Ann. Rev. Biomed. Eng. 1999, 1, 505-534). Thus, the skilled artesian would be expected to screen large number of crystallization conditions, which may include screening variety of conditions in space, a micro gravity environment. A protein which may crystallize under specific crystallization condition, it mutants may or may not crystallize under the same condition. In many cases, a protein that can't be crystallized, one of its specific mutants might be crystallized. Even if a crystal is obtained, it may or may not be suitable for structure determination by X-ray crystallography. It should be noted that the word domain in the claim does not define the boundaries of the protein to be crystallized, and the protein that was used in obtaining the crystal is not a native amino acid sequence of the extracellular domain. Thus, searching for a crystallization conditions for a protein and its complexes that is suitable for X-ray crystallography is well outside the realm of routine experimentation and predictability in the art of success in is extremely low. The amount of experimentation to identify an orthorhombic crystal for a protein having amino acid sequence containing any mammalian extracellular domain of DPP-IV, or any insertion, deletion or addition mutant thereof in space group $P2_12_12_1$ suitable for structure determination X-ray crystallography is enormous. Since routine experimentation in the art does not include screening large number of crystallization conditions or mutants of any mammalian DPP-IV extracellular domain which can be crystallized where the expectation of obtaining the desired crystal in space group $P2_12_12_1$ is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the exact amino acid sequences of the extracellular domain of DP-IV, the chemical structure of a ligand which can bind to said domain and form the binary complex to be crystallized in space group $P2_12_12_1$, and identify a crystallization conditions that produce a crystal suitable for structure determination by X-ray crystallography. Without such guidance, the experimentation left to those skilled in the art is undue.

> The following is a quotation of the second paragraph of 35 U.S.C. 112:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "extracellular domain of mammalian DPP-IV" in claims 1, 4, 7, and 9-12 renders the claims because the resulting claim does not define the metes and bounds of the claimed invention. The phrase is not defined in the specification, the art contains different fragments described as the extracellular domain, and one of ordinary skill in the art would not know which of the various fragments in the art read on the claims. For example, see US 2005/0260732 which define the domain as residues 33-766 of the human enzyme. For examination purposes only, the phrase is assumed to mean any fragment of DPP-IV from any

mammalian source having catalytic activity. Claims 2, 3, 5, 6, 8, 13 and 14 are included in this rejection because they are dependent on a rejected claim and do not cure its deficiencies.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by U. S. published application US 2005/0260732 ('732), which claim priority to provisional U. S. application 60/398,761, filed on July 29, 2002. The provisional applications is in Japanese fully support the claimed invention.

The '732 document teach the crystallization of water-soluble human dipeptidyl peptidse IV (DPPIV) residues 33-766 comprising the extracellular domain with a histidine-tag attached to the C-terminus, see page 14, paragraph 203. It describes an orthorhombic crystal in space group $P2_12_12_1$ under the conditions cited in paragraphs 220 and 221. The crystal contains two molecules (one homodimeric) per asymmetric unit. See paragraph 235. Thus, the crystal of DPP-IV described in the '732 document meets all the limitation of claim 1 of the instant application.

Claim 20 is allowed over the prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTWTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen M. Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1656